Gut fermentation: a reappraisal of an old clinical condition with diagnostic tests and management: discussion paper

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Introduction

This paper is concerned with a group of patients well known to every clinician: those with a 'thick folder'. These unfortunates have usually been seen in several departments. Copious, often expensive investigations have been carried out and almost invariably normal results are recorded, with the result that by default a psychiatric diagnosis is usually made. Further the common symptoms are often multi-organ and somewhat indefinite, namely; fatigue, musculo-skeletal aches and pains, abdominal discomfort, bloating, changed bowel habit and catarrhal discharge.

Recent studies reveal that many such patients can produce trace levels of blood ethyl alcohol from small test doses of sugar given orally[1]. Data supporting this contention will be found given later. Testing for alcohol has now been carried out on a number of patients with the above symptoms, and in view of the encouraging results obtained, a small group of practitioners gathered for two *ad hoc* meetings at the Royal Society of Medicine on the 15 and 28 March 1990. This paper represents a review of the subject and the discussions which took place, and sets out a programme for future investigation. We are provisionally terming the condition 'gut fermentation'.

Historical parallels

In studying this condition it is clear that similar conditions have been described previously. The term 'carbohydrate dyspepsia' was coined by Hurst[2] in 1931 and was subsequently reviewed in the standard medical texts of the time up to the 1970s[3-9]. By 1976 the condition was being viewed differently. Berk, writing in Bockus' *Gastroenterology*[4], describes the patients as 'essentially unhappy individuals' and gives the following clinical description. 'Any suggested panacea and therapeutic straw is grasped. No regime is too severe, and no program too forbidding. With the tenacity of the faithful they grope their way from one physician to the next in a relentless search for a permanently successful remedy'. Thereafter, the condition of carbohydrate dyspepsia otherwise known as intestinal carbohydrate dyspepsia or even carbohydrate intolerance[10], appears to have been considered as a psychological response rather than an organic syndrome.

In 1978 Truss[11-13] and subsequently Crook[14] put forward a concept of *Candida* intoxication, otherwise termed chronic candidiasis sensitivity syndrome[15]. This concept remains unproven and has never been the subject of adequate studies.

Nevertheless, there are parallels which merit review. The workers in the 1930s restricted carbohydrate intake (also legumes) and used betaine hydrochloride, pancreatic enzymes, *Lactobacillus acidophilus* preparations and vitamin supplements in therapy. The same measures have been proposed in chronic candidiasis sensitivity syndrome and by some workers attempting to control gut fermentation. These may or may not be the same or indeed signify gut fermentation as a syndrome.

What are the symptoms?

In recent years a wide variety of symptoms have been alleged to be related to the above condition. If all were to be accepted there would be a danger of claiming the condition to be a universal explanation for all illness. If only core symptoms, usual in all patients, are accepted the list would still have weaknesses: no single symptom only occurs in this condition and there is a wide differential diagnosis. The following provisional list was agreed subject to further study.

Psychological

Poor concentration, poor short term memory and lethargy. Brain 'fag' was held to be highly relevant, but the term requires explanation. The subject experiences a feeling that thinking is difficult and described as wading through treacle, or a mind obstructed by cotton wool. Thought can be completed with difficulty. It can be distinguished from the pattern seen in hyperventilation, where thought is flitting, disjointed and there is a rapid rush of ideas.

Musculoskeletal

There is a difficulty initiating physical activity. It was agreed that fatigue was doubtful and weakness not relevant.

Gut

Bloating, wind, altered bowel habit, perianal and/or vulval itch were agreed.

Respiratory tract 'catarrh'

Mucous discharge from the nose, or productive cough, whether or not associated with asthma, as well as recurrent sinusitis are symptoms present in both atopic and non-atopic subjects. If these symptoms are present in conjunction with those described above, the patient does not usually show positive immediate weal and flare skin tests. In this situation, the group were clear that a proportion of these subjects responded well to dietary manipulation and antifungal therapy.

General

The patients are often multi-organ polysymptomatic. They have had numerous investigations which have

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shown no abnormality. They frequently have a 'thick folder'. They often have a craving for sugar. Food dislikes are not a feature. It was noted that symptoms of food intolerance, and of hyperventilation may show some common features. Clearly patients with gut fermentation may also have these problems or may have been misdiagnosed.

Does a syndrome exist?

It was agreed that a distinct nosological entity appears to exist.

What do we call it?

Earlier writers have used the terms intestinal carbohydrate dyspepsia[2-5], carbohydrate indigestion[6] or even carbohydrate intolerance[9]. To revive one of these terms has the merit of historical continuity. However, there is a considerable change of emphasis in the approach of Truss[11-13] and Crook[14]. The terms they use, and later variations such as chronic candidiasis sensitivity syndrome[15] all carry the implacation that *Candida* has been proven to be the cause, and this is not so. Therefore, any name including *Candida* must at present be unacceptable. Listed below are details of a test for the condition which depends upon the production of ethyl alcohol following a sugar load. We agreed that it would be appropriate to use a new name based on this finding, and we therefore proposed gut fermentation.

Bacteriology

It has been claimed that nystatin or amphotericin given to these patients results in benefit. Because these drugs have a primary antifungal action, this has led some to the conclusion that this establishes a fungal cause for the condition. However nystatin and amphotericin have biological actions separate from their polyene antibiotic action by stabilizing (immobilizing) cells in gut wall membranes, and if these drugs are shown to be effective in treating the condition it does not necessarily follow that this proves that *Candida albicans*, or indeed any other yeast, is necessarily the cause of the condition[16,17].

Examination and investigations

As many have found routine clinical examination, standard laboratory tests and radiological examination reveal nothing that is specific to gut fermentation. In particular, cultures for *Candida albicans* will reveal positives in patients who are well, and will fail in patients who are symptomatic since *Candida* is a normal commensal organism[16,17]. Ethyl alcohol as fermentation appears to be part of this condition and a search for metabolites of this fermentation process might be useful with ethyl alcohol a likely candidate for study[18]. The test protocol[1] is as follows: fasting subjects provide a baseline blood sample for blood glucose and alcohol, and then receive a test dose of IG glucose in a hard gelatine capsule accompanied by 4G of glucose to ensure passage to the small bowel. A repeat blood sample is drawn after 60-65 min. Control subjects do not show an increase in blood alcohol (Table 1) but increases in blood alcohol levels are found in patients usually of the order of 1.0-7.0 mg/dl (Table 2).

Further work has shown that levels are subsequently lowered in patients who have received treatment.

Hurst[2] proposed that for intestinal carbohydrate fermentation a faecal fermentation test was diagnostic.

*Table 1. Blood glucose levels for normal subjects**

	Initial glucose	*Final glucose*
n	30	30
Mean (mmol/l)	4.11(m 4.13 f 4.08)	4.35(m 4.38 f 4.32)
SD	0.27	0.31
SE	0.05	0.06
t-paired (two tail)	$P<0.001$	
	Initial alcohol	Final alcohol
Alcohol (mg/dl)	<0.50	<0.50

*12 male and 18 female subjects; age range 19-65 years; mean±SD 35±7.2 years

Table 2. Treatment of alcohol test positive patients (n=241)

Method of treatment	*Number*	*Alcohol test negative (on retest)**
Diet alone	64	27
Diet and antifungals	149	116
Diet and broadspectrum antibiotics	28	2

*At 8-18 weeks

Sometime it would be appropriate to compare the results of the gut fermentation alcohol test with faecal fermentation, as this would show whether or not the two are related conditions (Figure 1).

Patient management

This area remains controversial and unresearched, some dietary restrictions, usually of fermentable simple sugars and refined carbohydrates appear to be widely practiced, but there is no agreement on the precise regimen which is ideal, and indeed some physicians are currently employing a course of antifungal drugs (usually nystatin) without the use of any dietary programme. It was agreed that both diet and drugs were capable of systematic study (Table 2). The use of supplements would depend on laboratory assessment of deficiency. As in the 1930s and 1940s, hypochlorhydria and pancreatic enzyme deficiency are considered by some to be relevant. This requires laboratory investigation which has yet to be undertaken. Some of our forebears used supplements of *Lactobacillus acidophilus*[3] which is in vogue at the present time but many commercially available preparations are devoid of any activity.

Antifungal drugs need to be approached with caution. Earlier authors and current experience remind us that gut fermentation itself is not fatal. At least one preparation, ketoconazole, has been associated with irreversible liver damage[19] and it is obvious that if drugs are to be used, only those not associated with adverse reactions worse than the disease justify consideration. This too requires a properly conducted double blind trial, which has not yet been done.

There are no published critical studies of dietary manipulation and/or antifungal therapy available and further research is essential. There exists a single report[20] which presents the results of a randomised double blind trial for the candidiasis sensitivity syndrome. This carefully performed trial failed to show significant symptomatic benefit from systemic,

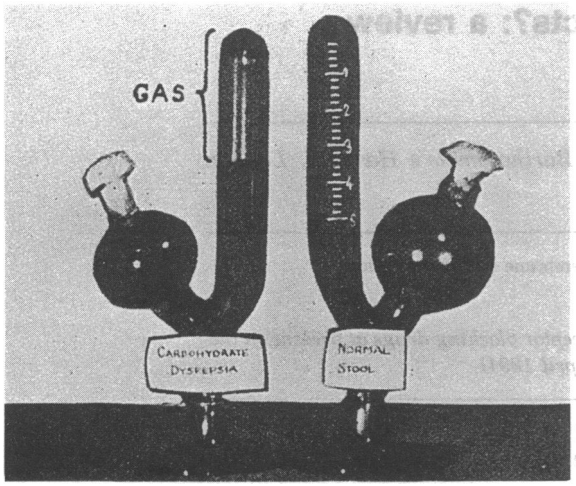

Figure 1. Carbohydrate dyspepsia (left) compared with normal (right) faecal fermentation tests applied to similar amounts of faeces. The left hand tube contains much gas, the right hand tube practically none[2]

vaginal or combined nystatin therapy. The trial is reviewed in an editorial in the same publication[21], where our attention is drawn to the weaknesses of the trial. The selection of patients may have been at fault, although this is unlikely. The lack of a washout period between active and following placebo may well have led to a carry over into the placebo period and would falsely elevate the apparent benefits of any placebo regimen. However, the gravest reservation must be that diet was completely uncontrolled and the experience of our group seems to suggest that, without control of starchy foods, no improvement will be seen. However this trial does seem to resolve the question of whether antifungals alone are an appropriate approach to therapy: it would seem they are not.

What research needs to be done?

The answer to this question is that no aspect of the condition (aetiology, definition, symptomology, investigation or management) has so far adequately been covered and for most, not a single satisfactory published paper can be quoted. Filling this vacuum cannot take place other than slowly. If this present work is allowed to set out some details of terminology, certain areas do present themselves for immediate study and are now being undertaken.

(a) Documentation of presenting cases, monitoring results with gut fermentation alcohol studies and repeated symptom questionnaire findings before and after treatment.

(b) Small bowel biopsy and gastrointestinal microbiological studies are needed, as we have no knowledge as to where the fermentation process takes place and what cause(s) may be operating, although from the gut fermentation alcohol test, the small intestine seems to be the organ affected.

(c) Nutrient abnormalities may be important and should be measured, with comparison between pre and post-treatment levels.

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